PATENT
Attorney Docket No.: UBC1180-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Hancock et al.	Art Unit:	1654
Application No.:	10/661,471	Examiner:	M.A. Audet
Filed:	September 12, 2003	Conf. No.:	7167
Title:	EFFECTORS OF INNATE IMMUNITY DETERMINATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

I, Oreola Donini, Ph.D., do hereby declare and state that:

1. I presently hold the position of Senior Director of Preclinical Research and Development at Inimex Pharmaceuticals Inc.

2. I hold a Ph.D. in chemistry, focused in small molecule chemistry and discovery granted by Queen's University in Kingston, Ontario.

3. I have worked in the pharmaceutical industry performing preclinical research and development of small molecules, small molecule discovery, cheminformatics, molecular modeling, and chemistry for the past 7 years. Prior to entering the pharmaceutical industry, I was a post-doctoral fellow at the University of California, San Francisco, performing research on lead optimization of MMP ligands and determination of enzymatic mechanisms of action for citrate synthase. A copy of my curriculum vitae is attached as Exhibit C.

4. The University of British Columbia is the assignee of U.S. Application Serial No. 10/661,471, filed September 12, 2003, entitled EFFECTORS OF INNATE IMMUNITY DETERMINATION.

5. U.S. Application Serial No. 10/661,471, filed September 12, 2003, is a continuation-in-part of U.S. Application Serial No. 10/308,905, filed December 2, 2002, currently pending, which claims the benefit under 35 U.S.C. §119(e) of U.S. Application Serial No. 60/336,632, filed December 3, 2001.

6. I am familiar with the contents of the above-identified application, and have reviewed the Office Action dated April 5, 2007. I understand that the Examiner has rejected claims 99-100 and 106-107 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification allegedly fails to comply with the enablement requirement because peptide SEQ ID NO:7 has allegedly not been shown to have any anti-inflammatory activity, anti-septic activity, or immune system stimulation, alone and absent the antibiotic or granulocyte-macrophage colony stimulating factor (GM-CSF).

7. I also understand that the Examiner has rejected claims 93 and 99-104 under 35 U.S.C. § 112, second paragraph, as allegedly being unclear when comparing claims 93 to claims 105-110 (directed to a method of stimulating innate immunity in a subject having or at risk of having an infection comprising administering to the subject GM-CSF in combination with peptide SEQ ID NO:7).

8. I also understand that the Examiner has rejected claims 102 and 109 under 35 U.S.C. § 112, second paragraph, as allegedly being unclear where the cyclization of SEQ ID NO:7 is to be perfomed.

9. Attached hereto as Exhibit A is a scientific publication (Scott et al., Nature Biotechnology, 25: 265-472 (April 2007)) showing anti-infective peptides including SEQ ID NO:7 that selectively modulate the innate immune response along with their mechanism of

action. Scott et al. shows that SEQ ID NO:7 is protective in a broad range of *in vivo* infection models by local and systemic administration, and that SEQ ID NO:7 is not directly antimicrobial but acts instead on the host innate immune system. Additionally, evidence of the mechanism of action of SEQ ID NO:7 is presented showing that SEQ ID NO:7 activates several signaling pathways, stimulates transcription factors and sustains or enhances the levels of infection-clearing chemokines, while suppressing levels of pathogen-associated pro-inflammatory cytokines such as TNF-α without being toxic.

10. Attached hereto as Exhibit B is a report written by me presenting experimental data of a series of infection models.

11. The infection model studies presented in the report (Exhibit B) were undertaken between 2002 and January 2006 as part of the company's ongoing efforts to optimize dosing regimes, and identify other peptides and molecules with similar biological activities for drug development purposes. The report demonstrates the efficacy of SEQ ID NO:7, and related peptides, as having anti-inflammatory activity, anti-sepsis activity, and in stimulating the immune system to confer innate immunity. Results of the infection models presented in the report are as follows:

A) SEQ ID NO:7 demonstrated efficacy in a number of infection models, with multiple pathogens, routes of administration and dosing regimes (See Exhibit B, Figures 1-5). Because SEQ ID NO:7 and the other cationic peptides presented in the specification do not function by direct bacterial killing, as discussed in Scott et al. (Exhibit A), the results of the infection models serve as an important demonstration of the ability of the peptide to induce a "protective" host response against a very acute and rapid infection.

B) SEQ ID NO:7 is capable of decreasing inflammation in *in vivo* infection models and acute inflammation models. Data in Figures 6-9 of the report clearly indicates that in addition to aiding in the resolution of infection, SEQ ID NO:7 and related peptides are simultaneously able to modulate inflammation.

C) SEQ ID NO:7 is expected to reduce sepsis as an extension of its anti-inflammatory activity. This is demonstrated by the upregulation of CCL5, a positive prognosticator of sepsis outcome in a clinical setting, and by the activity of the related peptide, SEQ ID NO:6 in a sepsis model. Both SEQ ID NO:7 and SEQ ID NO:6 are very similar and would therefore be expected to act similarly to reduce sepsis, in view of their efficacy in reduction of *E.coli* LPS induced TNF-α production shown in Table 4 of the specification as filed. Similarly, both peptides would have similar anti-inflammatory properties and similar ability to confer innate immunity to a host.

12. The report also clarifies the difference between methods of administering the peptide in combination with an antibiotic or in combination with GM-CSF (i.e. the difference between the invention of claims 93 and 105). Pages 6-8 of the report show infection models incorporating complementary use of an antibiotic with SEQ ID NO:7. When the host is unable to clear infection via its immune system, antibiotics are administered to directly target the bacteria. In a complementary therapeutic approach, SEQ ID NO:7 and related peptides can augment the host's innate defenses. This situation, where antibiotics alone are insufficient to eradicate an infection, is represented in animal models using sub-optimal dosing of antibiotics. Additionally, antibiotic administration is occasionally given prophylactically to patients at high risk for developing an infection (for example, patients which have undergone autologous stem cell transplantation are often given prophylactic antibiotics during their recovery period in addition to GM-CSF). Prophylactic administration of antibiotics, while necessary in some cases,

does increase the likelihood of engendering antibiotic resistance, limiting the lifetime of current antibiotics and creating "superbugs". Thus, in these situations, it would also be advantageous to administer SEQ ID NO:7 and related peptides, thereby inducing a more effective immune response. SEQ ID NO:7 is effective in immune-compromised situations. Animal studies using mice have been performed showing complementary use of antibiotic with peptide SEQ ID NO:7. The descriptions and conclusions of the studies are as follows.

A) Figure 12 of the report shows challenge of female ICR mice by injection with 1.8×10^6 CFU/mouse of *S. aureus* mixed with cytodex beads. SEQ ID NO:7 was administered intramuscularly 4 hours prior to infection. Vancomycin was administered subcutaneously 1, 6 and 24 hours after infection. Mice were euthanized 48 hours post-infection and bacterial counts in the thigh were determined. The results showed those mice treated with peptide and vancomycin had bacterial counts about 5 (Log CFU/thigh) while those mice treated only with vancomycin showed bacterial counts between 4-6 (Log CFU/thigh).

B) Figure 13a of the report shows challenge of female RAG1 mice (lacking T and B cells) by intraperitonial injection with *S. aureus* in 5% mucin. 4 hours later, mice were injected with either saline or 24 mg/ml of SEQ ID NO:7. Mice were sacrificed 24 hours later and the bacterial load in peritoneal lavage fluid was assessed. The results showed that those mice injected with saline to have bacterial loads of about 1.0×10^6 CFU/ml while those treated with SEQ ID NO:7 had loads of about 1.0×10^4.

C) Figure 13b shows challenge of female CD1 mice rendered neutropic by treatment with 200 mg/ml cyclophosphamide 4 and 1 day before intraperitoneal infection with *S. aureus* in 5% mucin. 24 mg/ml of SEQ ID NO:7 was

administered 4 hours after infection and survival was assessed at 24 hours. The results show 40% survival of mice untreated after infection with *S. aureus*, while those being treated showed a survival rate of 80%.

13. In view of the present specification, and given the knowledge in the chemical arts at the time of filing, one skilled in the art would have understood that the peptides described in the specification would be capable of being cyclized by a number of standard methods. For example, cyclization could be performed in a 'head to tail' fashion via the N and C termini, or as described in the specification by addition of 2 or more cysteine residues and subsequent oxidation to form disulphide bonds.

14. In view of the present specification, and given the knowledge in the immunological arts at the time of filing, one skilled in the art would have understood that the peptides described in the specification in light of their shown capacity to reduce pathogen mediated TNF-α production and to regulate various immune response pathways, would be capable of exhibiting anti-inflammatory activity, anti-sepsis activity, and conferring innate immunity. Given the links between infection and the inflammatory response and sepsis, one of skill in the art would have understood that the inventors were in possession of the complete invention without further undue experimentation.

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15. I further declare that the statements made herein of knowledge are true and that all statements made on information and belief are to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Oct 4, 2007

Oreola Donini
Oreola Donini, Ph.D.

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